Trichomoniasis in Adolescents: Unsuspected and Neglected

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Ode to the south

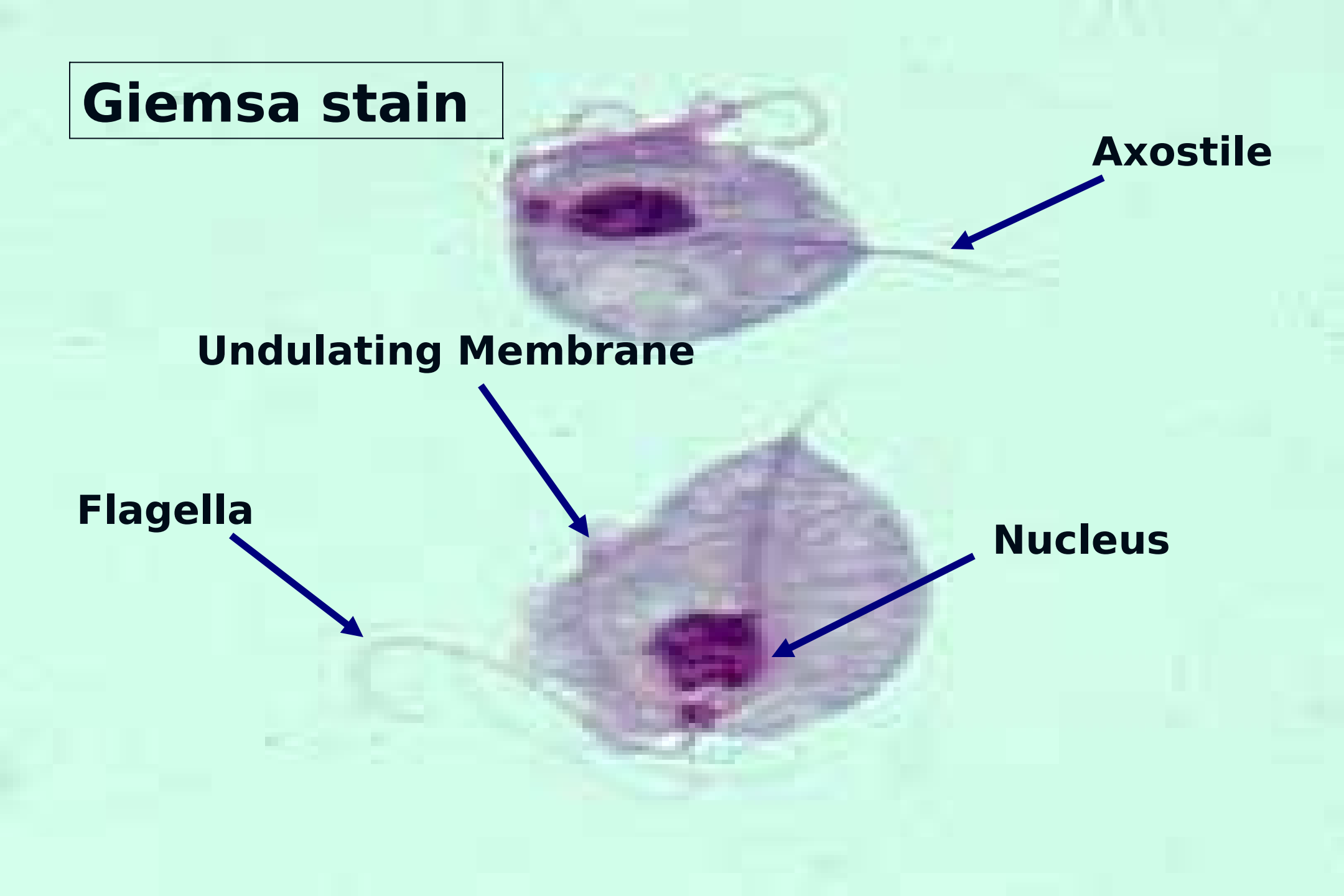
“Ever since locating here in the south
I have had barbecue sauce on my mouth”

Roy Blount, Jr.

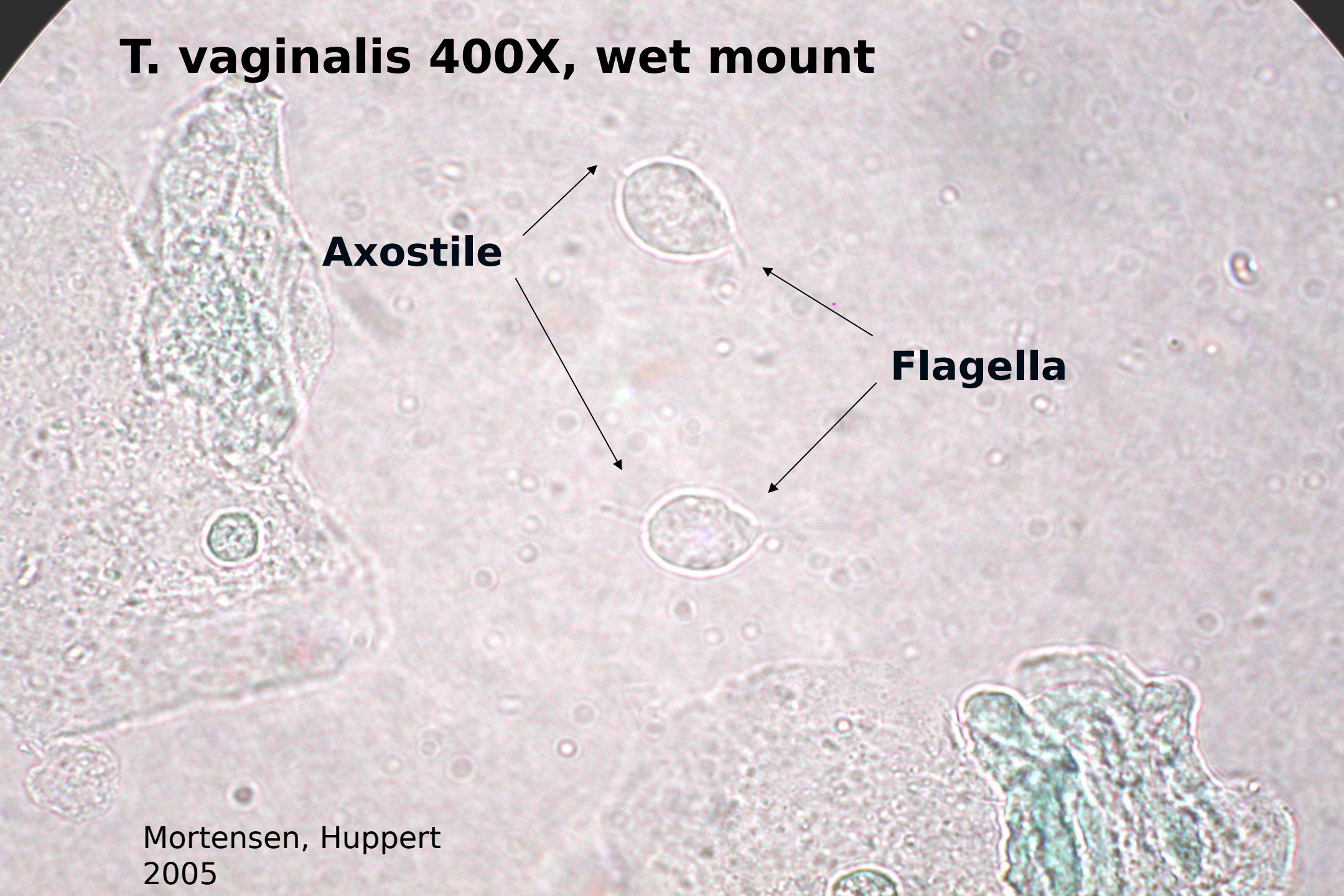
Objectives

- Review Pathobiology of *Trichomonas vaginalis*
- Evaluate prevalence of TV infection
- Discuss outcomes associated with TV
- Compare diagnostic methods
- Update on research in Adolescent Women
- Future directions for research and practice

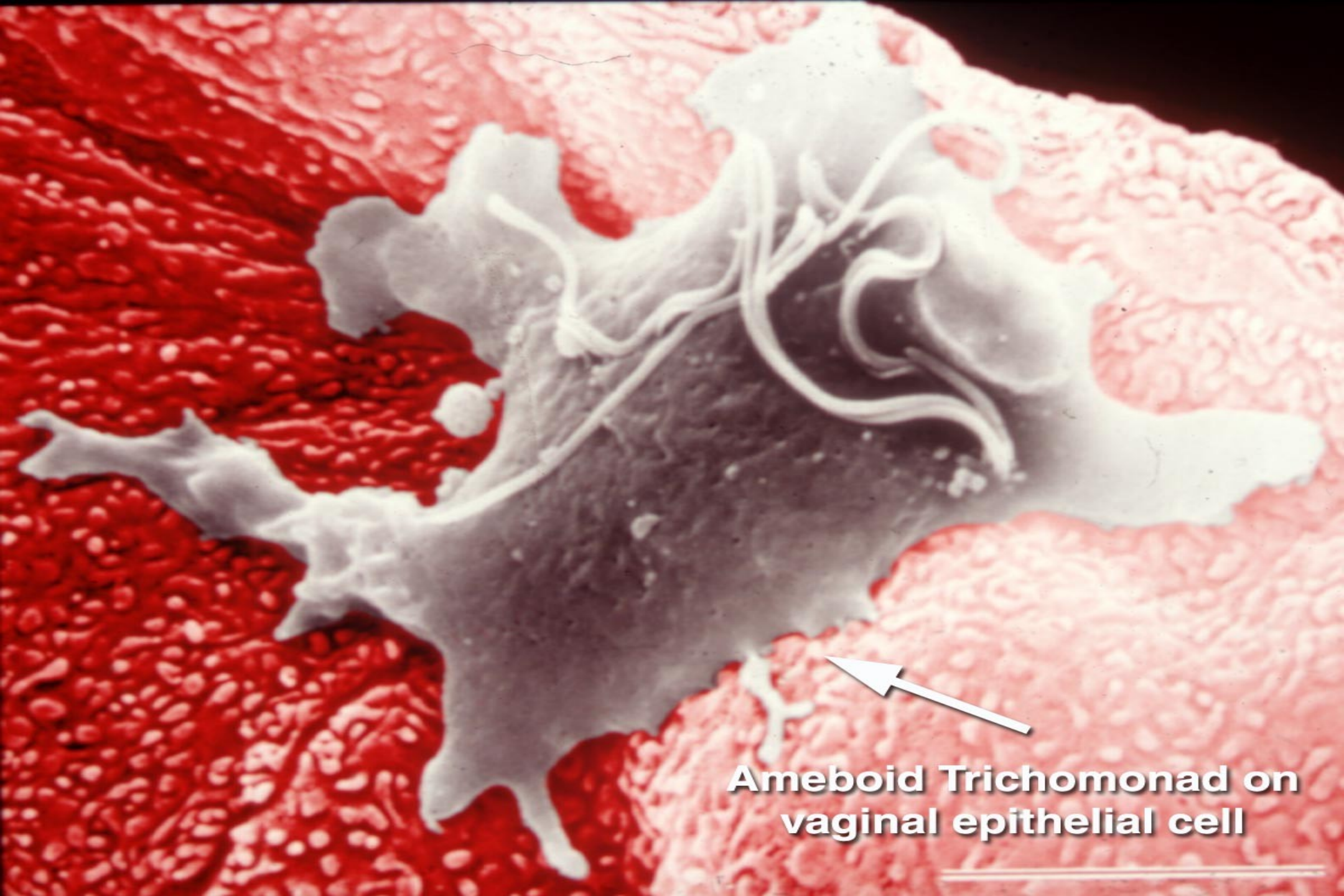
Giemsa stain



T. vaginalis 400X, wet mount



Mortensen, Huppert
2005


Ameboid Trichomonad on
vaginal epithelial cell

Trich pathobiology

- Inoculation
- Adhesion
- Local damage
- Inflammatory response
- Prolonged survival:
  - Alter host flora and pH
  - Avoid immune detection
  - Acquire nutrients

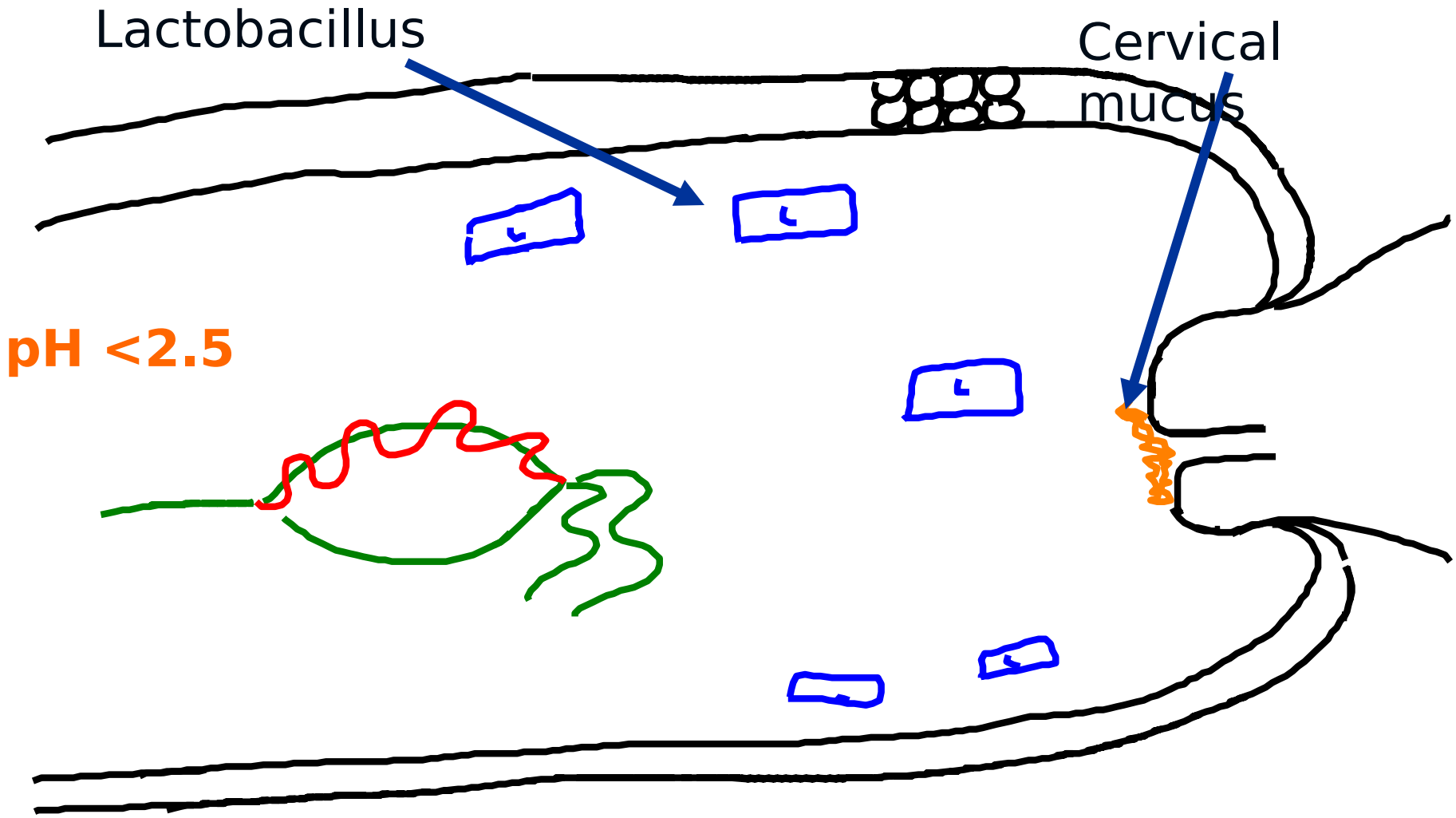
Petrin,1998

Inoculation

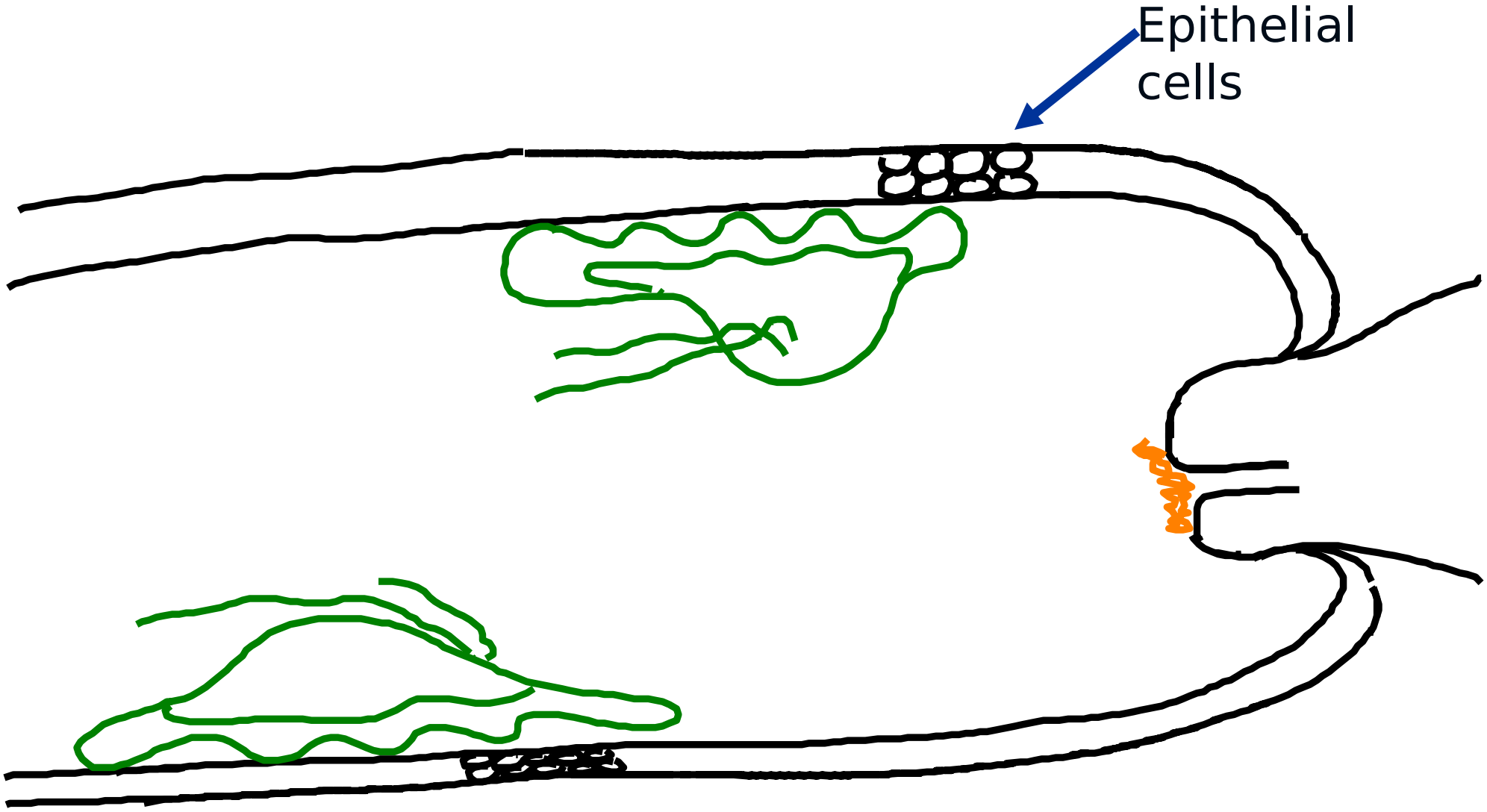
- Sexual contact
- Incubation 4-28 days
- Long duration of infection
  - 4 months in men
  - 5 years in women (Bowden, 2000)
- Prevalence increases with age

Transmission

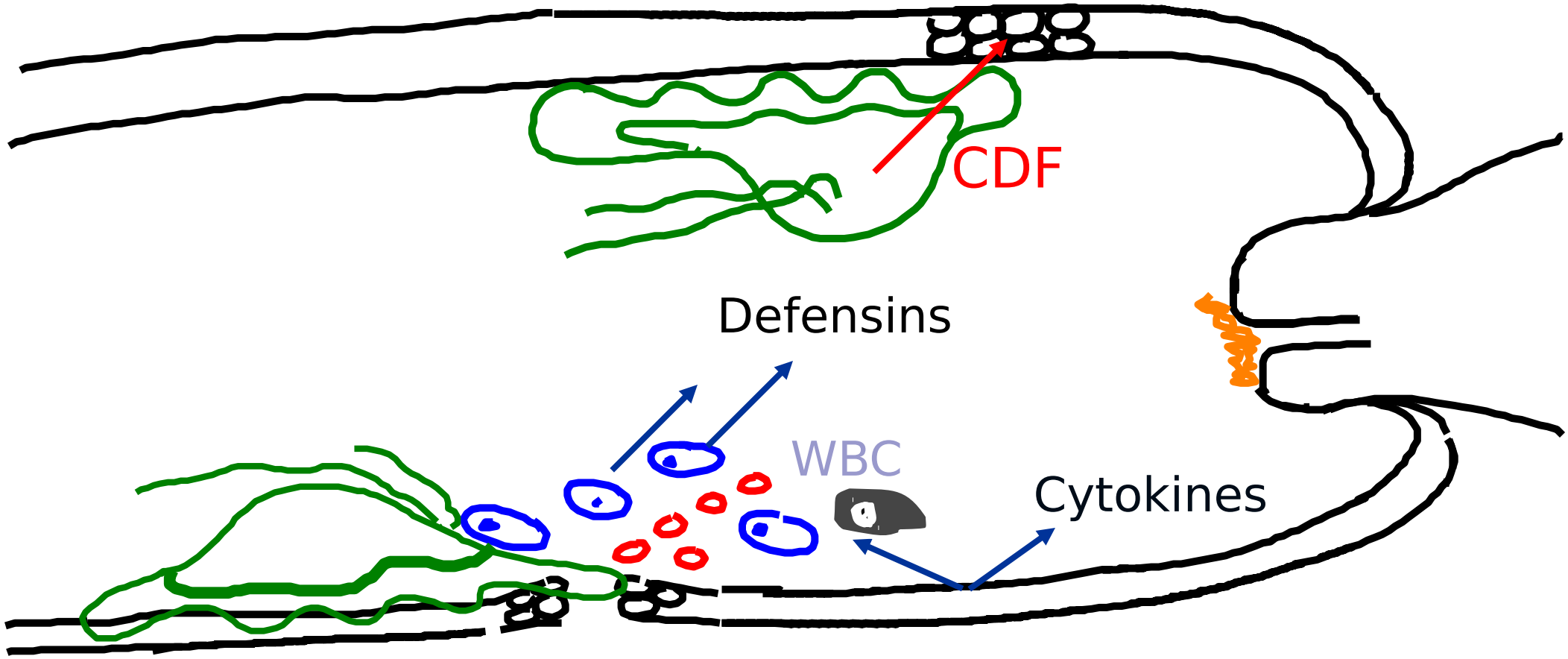
- More easily transmitted than CT, NG, HIV….
- Male to female: 85%
- Female to male:
  - 20-60% (Krieger, 1995)
  - 70% (Sena, 2003)



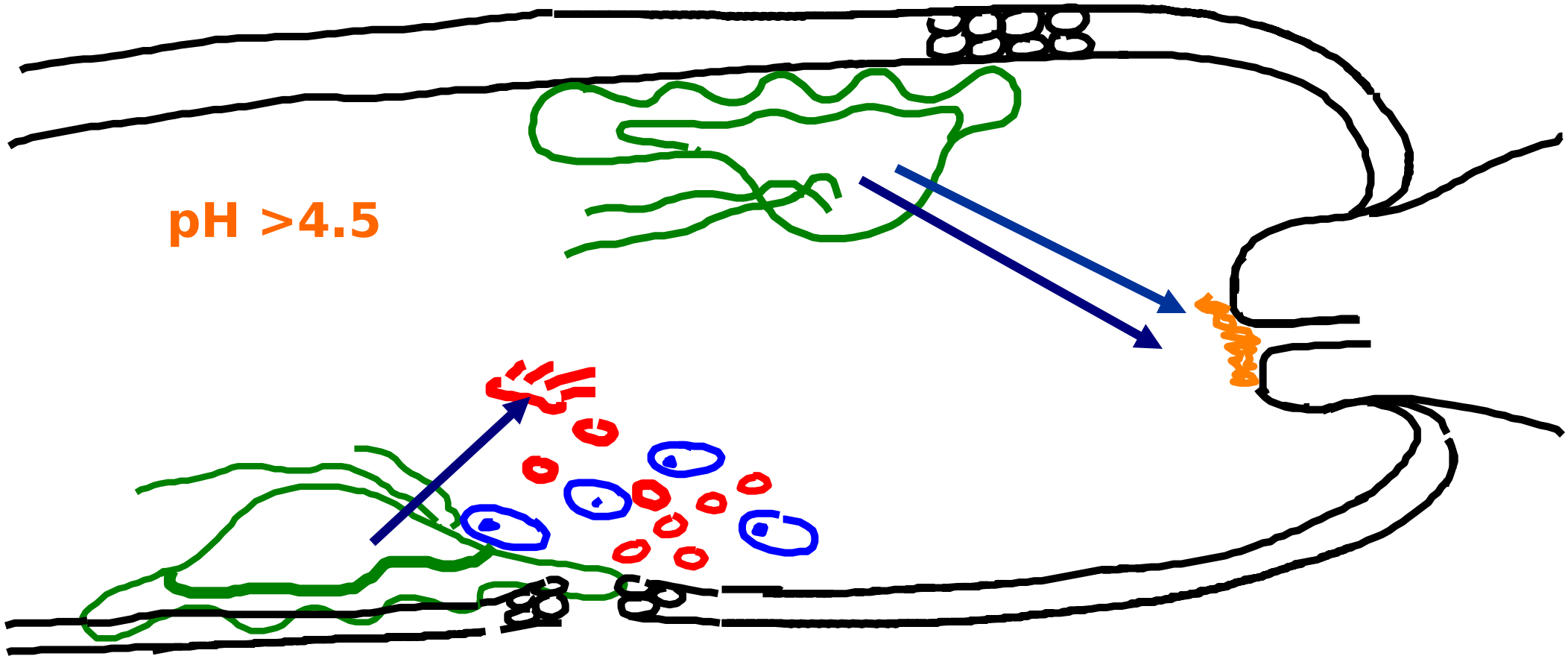
Trich inoculates the vagina



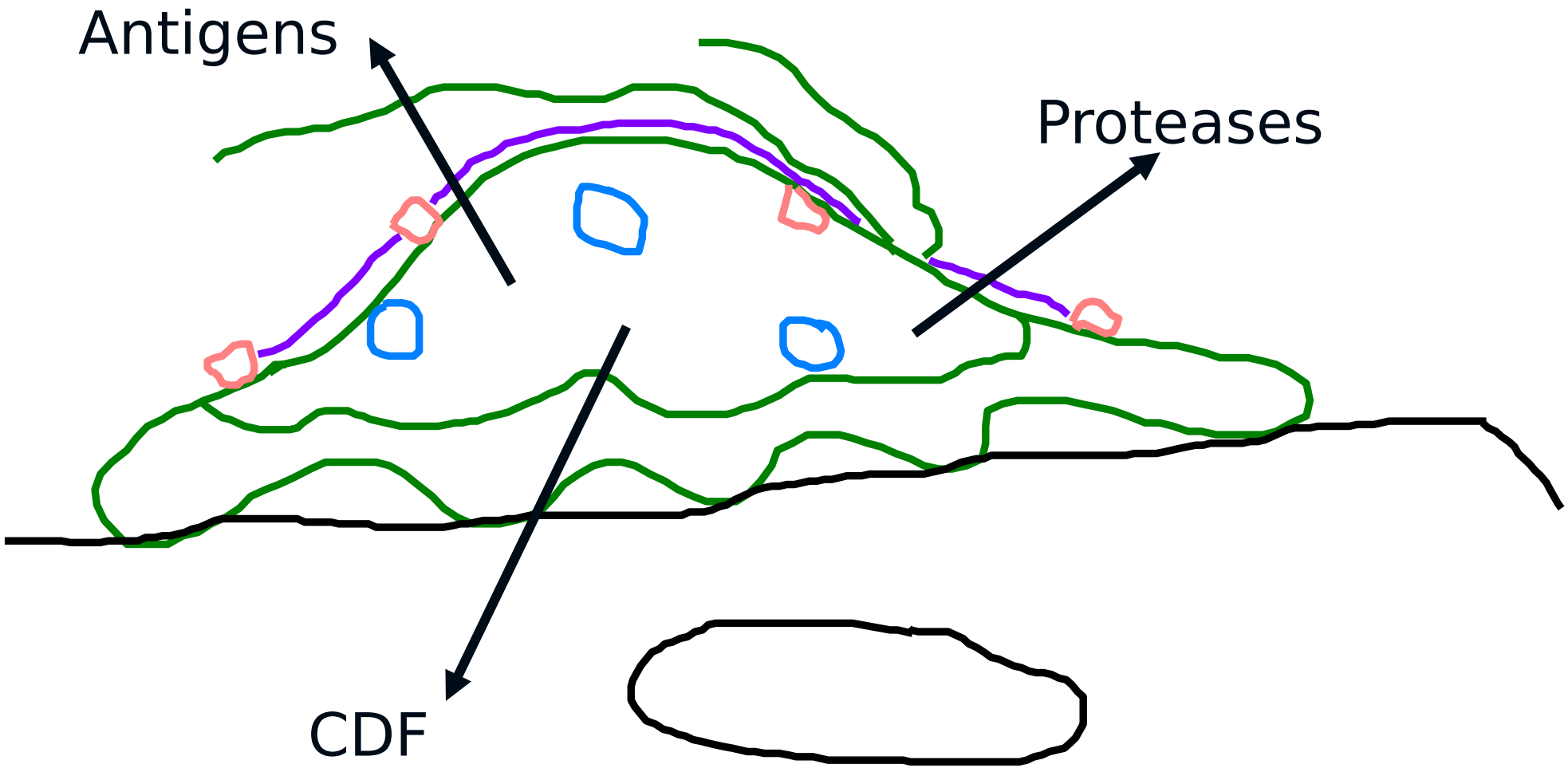
Trich adheres to the vagina



Local Damage and Host response



Acquire nutrients



Trich: attached and persistent

Trich: Highly prevalent

- Most common non-viral STD
- More common than CT and GC
- Worldwide > 180 million cases / year
- US estimated 7.4 million cases in 2000

Cates, 1999

Weinstock, 2004

Prevalence estimates are limited by:

- Rare population testing (1 study)
- No reporting requirements
- No tracking of in-office tests
- No screening guidelines
- Low sensitivity of usual diagnostic method (wet mount)

Trich prevalence (cont):

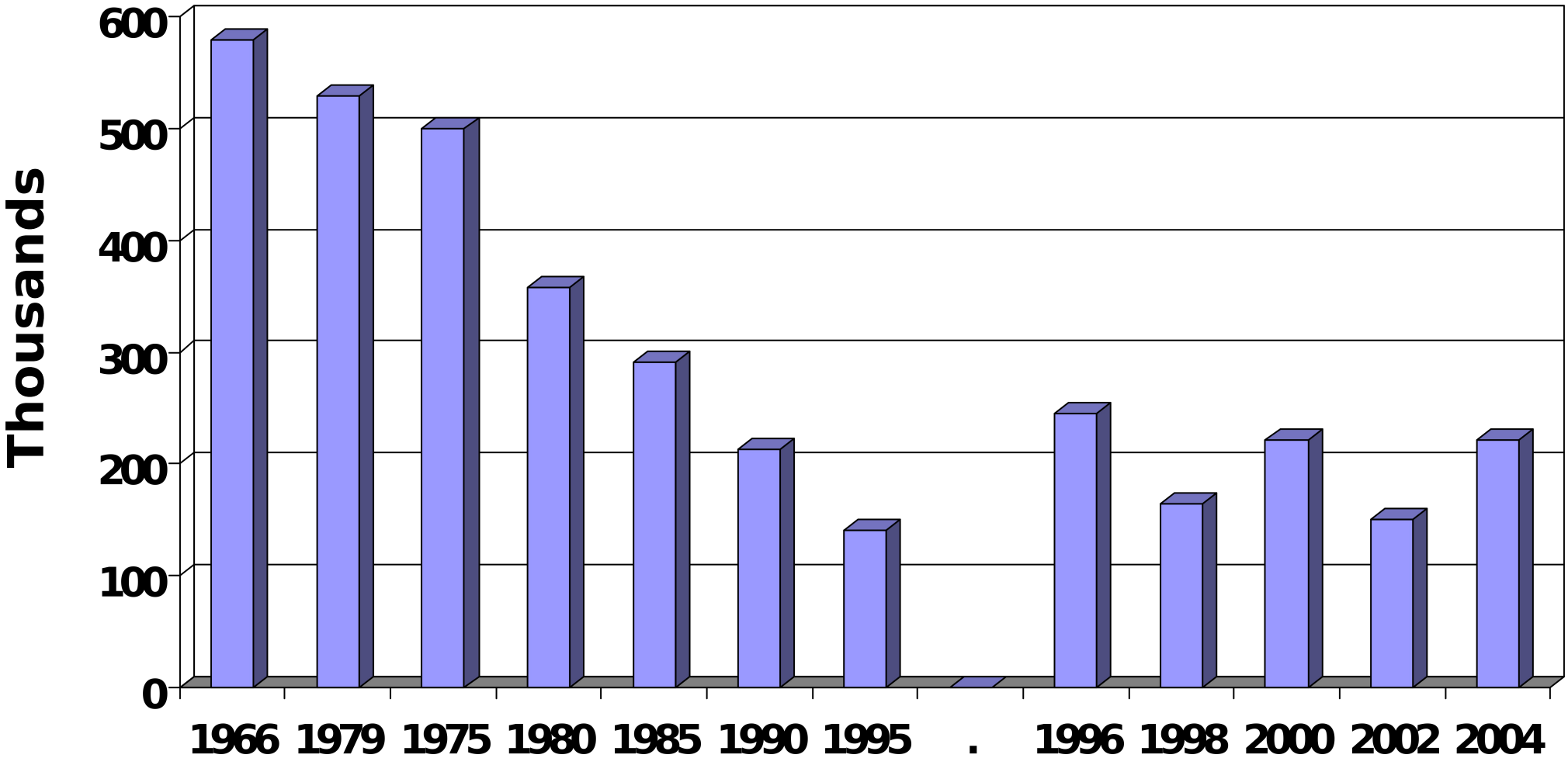
- No screening guidelines
  - Asymptomatic subjects not tested
  - >50% of those infected with TV may be asymptomatic
- Low sensitivity of common diagnostic methods
  - Wet mount 60% sensitive
  - Pap smear 60% sensitive

Wolner-Hanssen, 1989

Weise,2000

Lara-Torre, 2003

TV prevalence, US women NDTI



CDC- Trends in STIs 2004

Tv Prevalence in US Young Adults

- National Long. Study of Adolescent Health
  - Wave 3, Age 18-26
  - N=12,449
  - Nationally representative
- Urine sample: PCR for TV,CT, GC
- Overall **2.3%** prevalence TV
  - CT: 4%
  - GC:0.5%

Miller,Swygard, Hobbs et al 2005

Tv Prevalence in US Young Adults

- Race/gender disparities:
  - AA women: **10.5%**
  - AA men: 3.3%
  - White men: 1.3%
  - White women: 1.1%
- Highest: Age>25: 4 %
- South: 2.8%
- >95% of those with TV denied symptoms

Miller,Swygard, Hobbs et al 2005

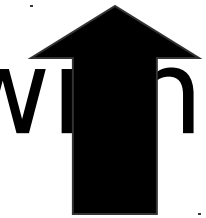
TV Prevalence in women

Population	Author,Year	**TV %**
Student Health clinic	Weisenfeld,2001 Smith,2001	**10** **13**
STD Clinic	Fouts,1980	**32**
	Kaydos,2002	**17**
	Huppert,2005	**29**
Prenatal clinic	Cotch,1997	**18**
Substance abuse	Bachman,2000	**43**
Prison inmates	Shuter,1998	**47**

Why care about trich?

- Cute
- Prevalent
- Persistent
- Associated with bad outcomes

In Women, TV associated with :



- **HIV**
- Risk of other STDs (**HSV**)
- Cervical neoplasia, **HPV**
- Tubal infertility
- Post-hysterectomy infection
- Atypical PID
- Preterm birth

TV and HIV: Prevalence

- In African cities, cross sectional study
  - Low HIV (4-8%) = Low TV (3-17%)
  - High HIV (31-35%) = High TV (29-34%)

- Pregnant Congolese:
  - HIV-: TV 10%
  - HIV+: TV 18.6%

Buve, 2001
Sutton, 1999

TV and HIV Acquisition

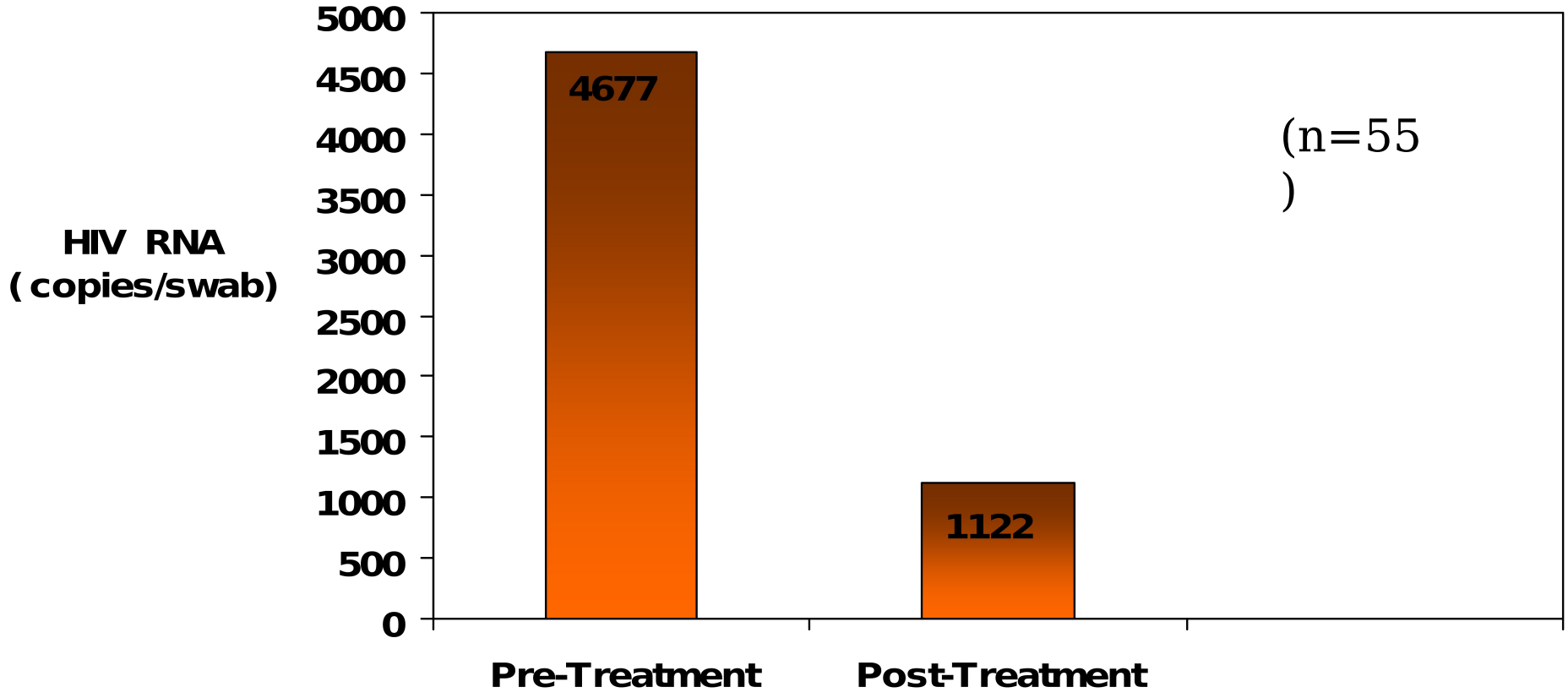
- TV associated with HIV infection
  - 431 HIV– women sex workers (Zaire)
  - With TV: OR HIV 1.9 (Laga, 1993)

- HIV associated with TV infection
  - 292 HIV+ women (US)
  - 10% annual incidence TV
  - cf 1-2% CT/GC (Minkoff, 1999)

TV as Risk Factor for HIV Transmission

- Marker for unsafe sex
- Increase susceptibility
- Increase infectiousness
- Alter normal flora and immune response

Treatment of *TV* reduces HIV in vaginal secretions



(Wang, 2001)

TV as a risk factor for other STDs

- GC (CT in Ad Health)
- HSV (new!)
- Cervical cancer (persistent HPV)

TV predicts GC

Study	Population	% with GC TV+ v TV -
Fouts, 1980	400 sx women	37 v 22
Wolner-Hanssen, 1989	779 women	31 v 11
Huppert, 2004	92 sx teens	61 v 17

P<0.01 for each study

TV and Herpes (HSV-2)

- Cross-sectional study
- 1780 women in STD clinic
- Tests for HSV-2 serology, CT, GC and TV
  - TV dx: WM or culture
- HSV-2 + serology higher in those with hx TV
  - 74 vs 44%, p<0.01
- Odds HSV-2
  - History TV: OR 1.6 (95% CI 1.2-2.2)
  - Current TV: OR 1.5 (95% CI 1.2-2.2)

Gottlieb, 2002

TV and HSV-2

- Longitudinal follow- up of those seronegative
- 646 females
- Incident TV increased risk of HSV
- Hazard ratio=3.7 (2.0-7.1)
- Controlled for age, race, enrollment site, condom use

Gottlieb, 2004

TV and Cervical Neoplasia

- Meta-analysis of 24 studies
- Summary relative risk was 1.93
- Most case-control studies had a positive association
- Limitations
  - Retrospective
  - Sexual risk behaviors
  - Other Infections

Zhang, 1994

TV as a Risk Factor for Cervical CA

- 19,114 Finnish women
- Mass screening program for cervical ca
- Pap diagnosis of HPV, Herpes, *TV*
- *TV prevalence* 8%
- Cervical cancer associated with
  - *TV* (OR=6.4)
  - HPV (OR=5.5)

Viikki, 2000

Trich Diagnostic Methods: Usual care

- Wet Mount
- Pap smear
- Limitations:
  - Low sensitivity 36-70%
  - Resources
  - Technical experience
  - Pelvic exam ?

Trich Diagnosis: Newer Methods

- Culture
- DNA probe
- PCR/ NAAT
- Rapid antigen tests

Trich Culture: InPouchTV

- Single pouch provides transport, cultivation and evaluation
- 85% sensitive 100% specific
- Self–obtained vaginal swabs can be used
- Long shelf Life
- Limitations:
  - Availability
  - 3- 5 days for final read

Borchardt,1997

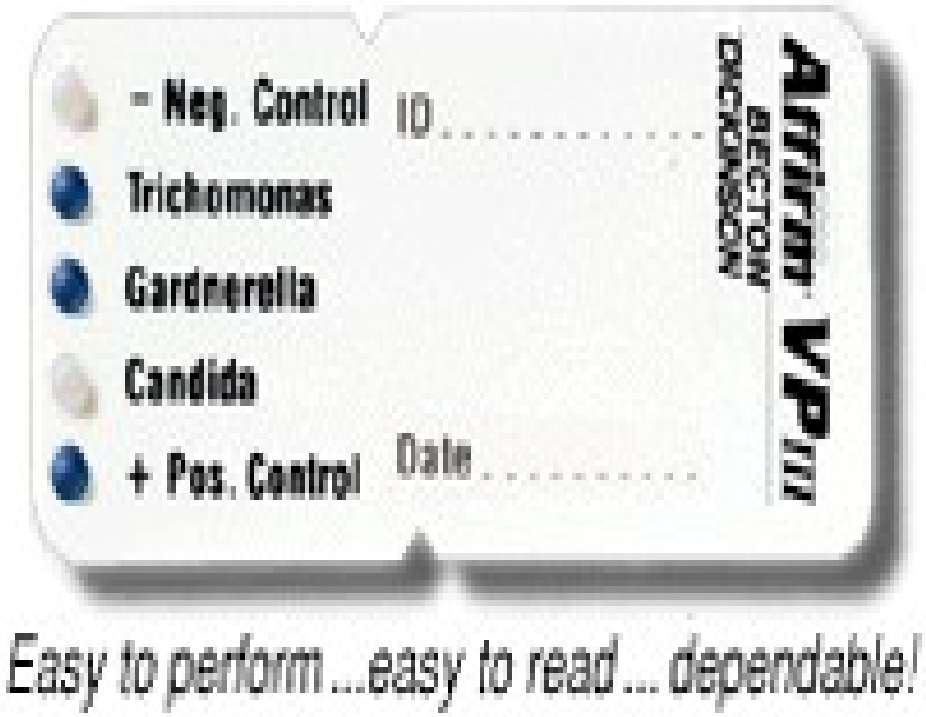
Levi, 1997

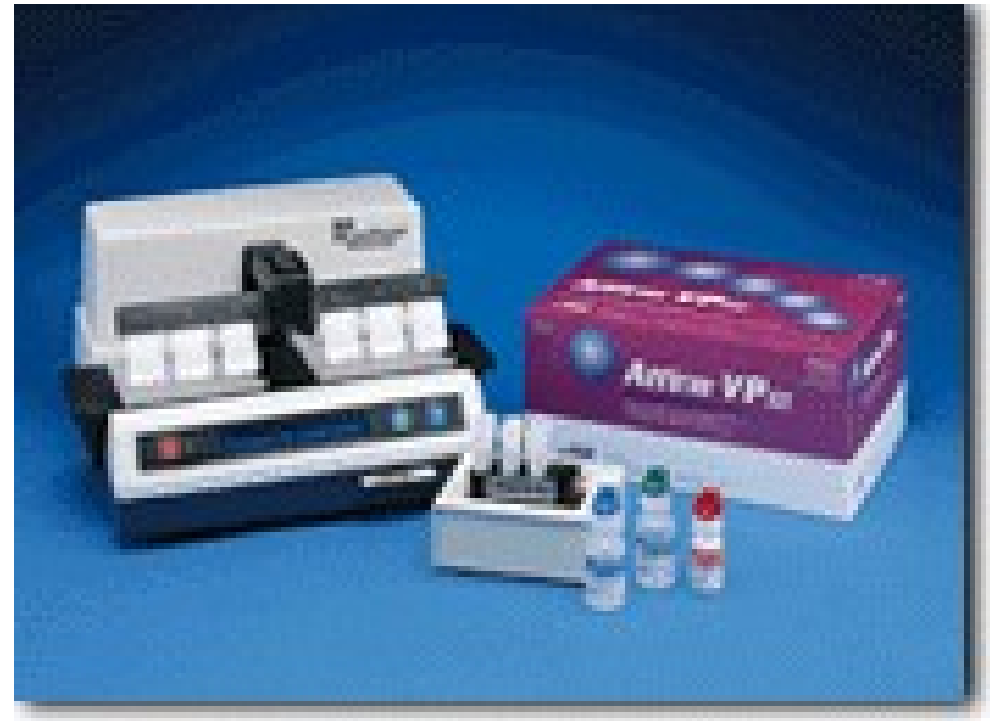
InPouch TV

Trich DNA test:

- AffirmVPIII (FDA approved 1997)
- Single sample for yeast, BV and TV
- 90% sensitive, 99% specific (DeMeo, 1996)
  - 44% sens cf to TMA (Sitay,2003)
- Limitations:
  - Cost
  - technology
  - “rapid” 45-60 min…

Affirm VPIII





Trich: PCR

- More sensitive than single culture
- Sensitivity 89-97%
- Specificity 88-97%
  - Depends on specimen source, primers, platform
- Limitations
  - Research lab settings
  - Cost and technology

Jordan, 2001, Crucitti 2002
Kaydos,2002, Kaydos 2003
Van der pol, 2006

Real Time PCR

- Really cool
- Gaydos, Hobbs
- 90% sensitive, 100% specific (urine)
- Expensive!!!!
- Time consuming

Hardick, 2003

Trich TMA

- Genprobe (Aptima) platform, primers, reagents
- Sensitivity 94-96%
- Spec 82-94%
- Abstracts only…

Trich Rapid Antigen Tests

- XenostripTV (FDA Oct 2002) replaced by OSOM® (FDA 2004)
- Immuno-colorimetric antigen detection
- Point of care
- 10 minutes

Rapid test research

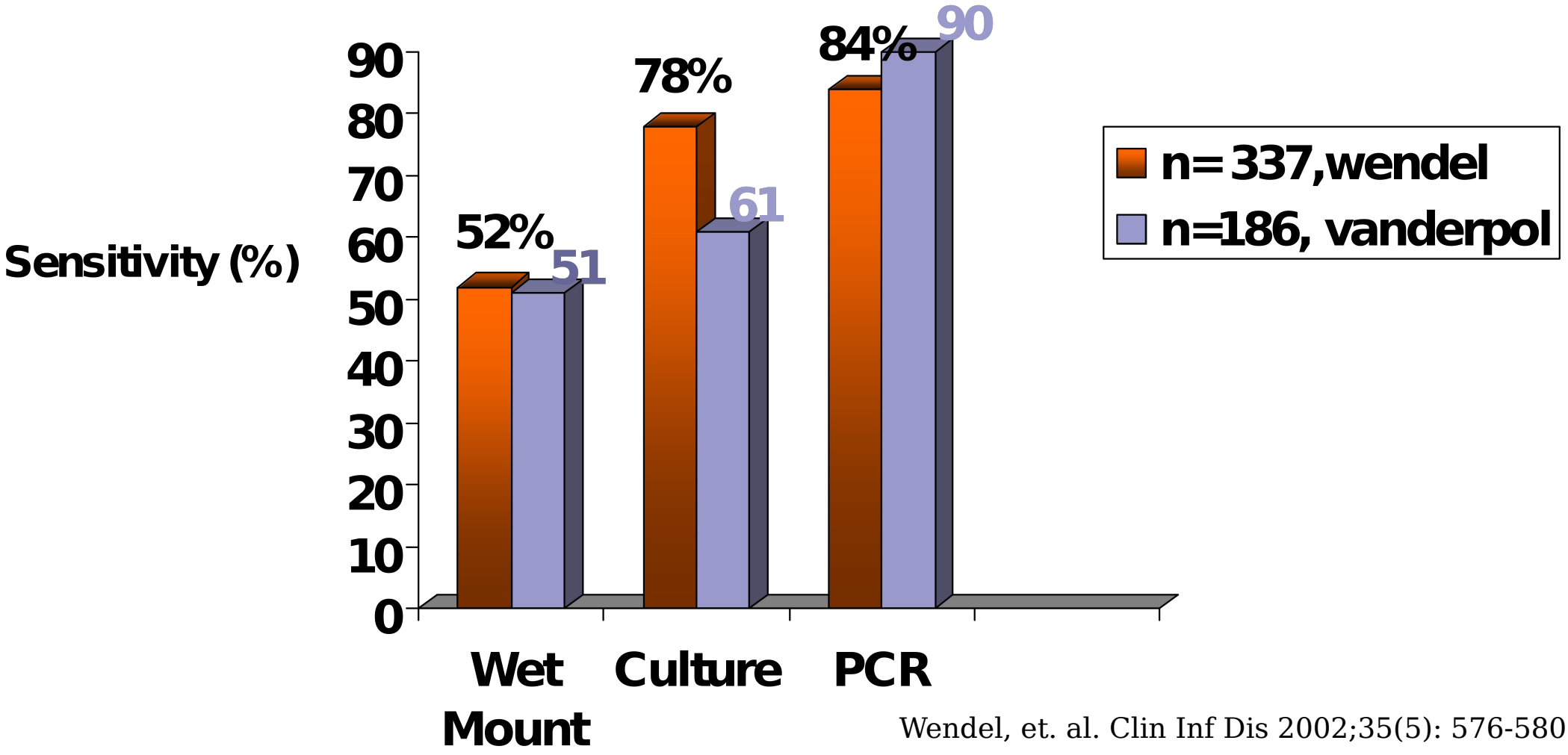
- Rapid test:
  - 83.3% sensitive
  - 98.8% specific
- Wet mount
  - 71% sensitive, set at 100% specific
- Rapid on used wet mount:
  - 75% sensitive, 98% specific

Huppert, et al, J Clin Micro, Feb 2005

Comparison of Diagnostic Methods

Method	Cost	Technical ease	Time to Results
Wet Mount	$	Easy	Minutes
InPouchTV™	$$	Easy	Days
Pap Smear	$$$	Moderate	Weeks
PCR	$$$$	Difficult	Hours-days
Rapid Antigen	$	Easy	Minutes

Diagnosis of *T. vaginalis* in Females:



Wendel, et. al. Clin Inf Dis 2002;35(5): 576-580

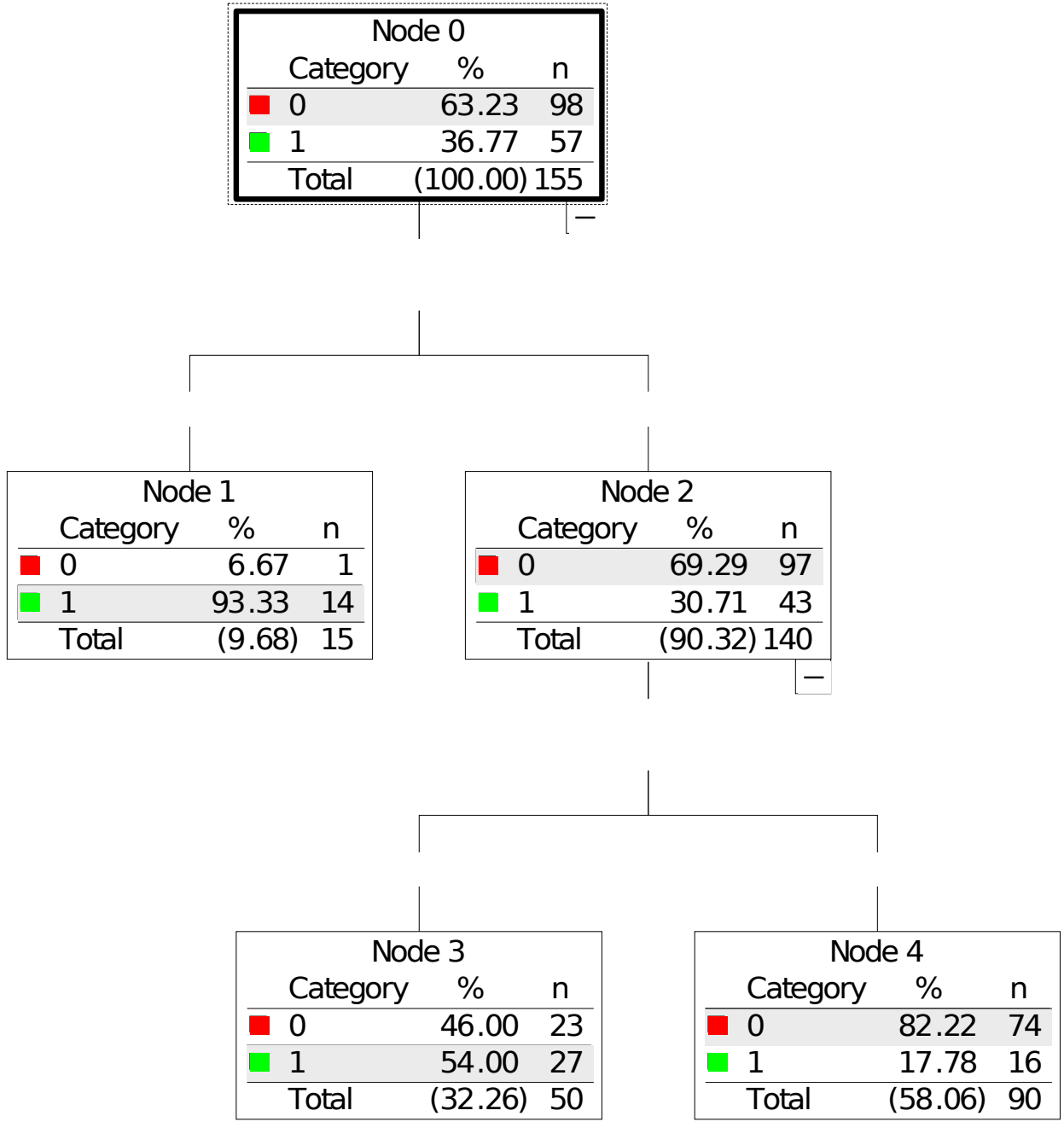
Research Update: Huppert

- STI UTI study: comparison of STIs and UTIs in teen females ± urinary and vaginal symptoms
- InPouch culture on all (some self collected)
- Results: (N=301)
- Overall Tv prevalence:18%
  - 12% in those who denied vaginal symptoms
  - **33%** with any vaginal symptoms

STI UTI study

- TV not associated with Urinary sx or UTI
- Predictors of TV: OR 95% CI
  - Vaginal symptoms 5.1 1.5-15.1
  - Urine LE+ 8.4 2.7-26.4
  - Urine Blood + 6.3 1.9-21.1
- Sterile pyuria= Tv or GC, not CT
- Wet Prep and UA recommended for females with urinary symptoms

CART



Sens: 74%

Spec: 76%

Huppert, In progress….

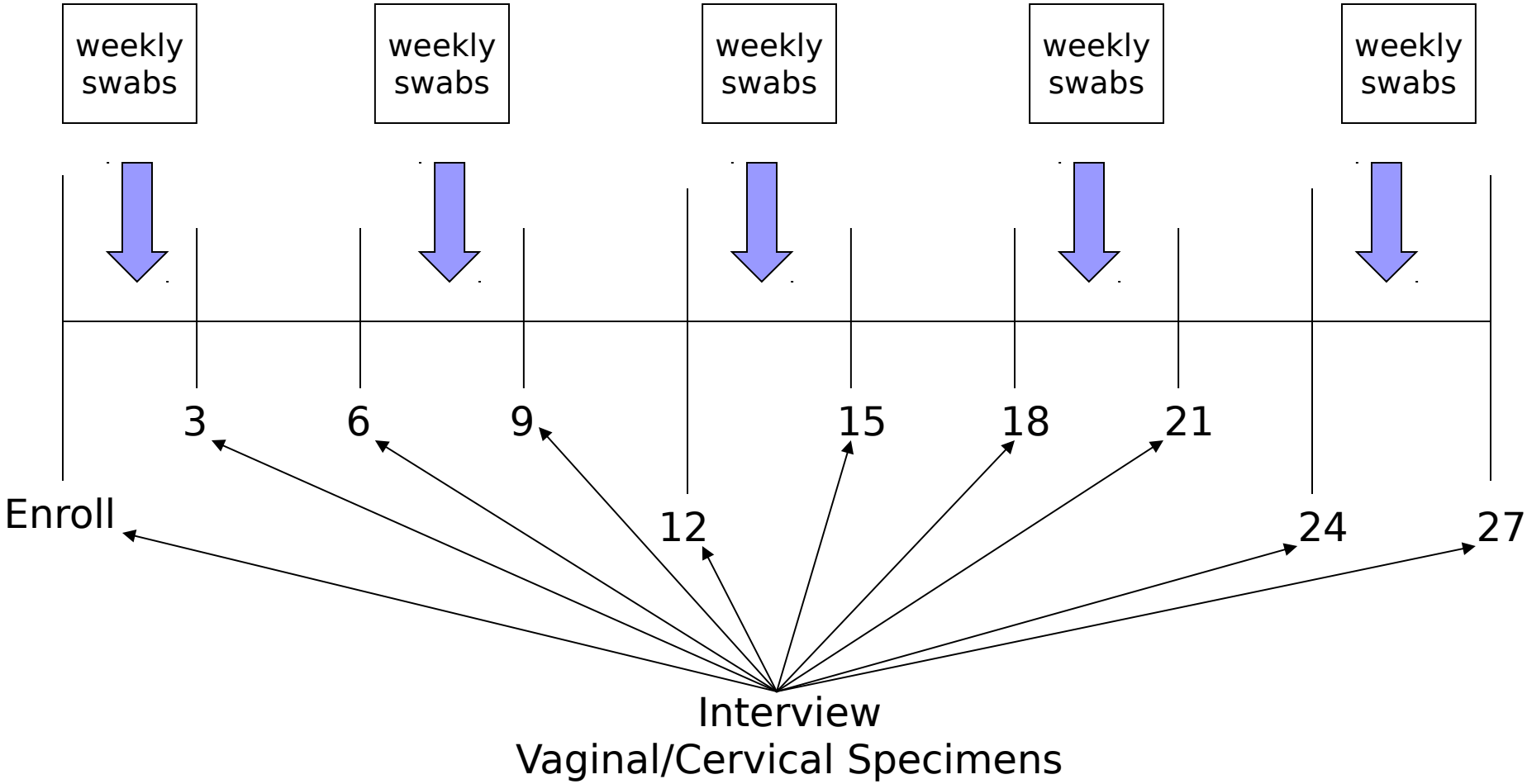
- Step-wise evaluation of wetmount , rapid test and culture in symptomatic adolescent females
- 359 adolescent females enrolled
- Overall **17%** prevalence TV
- Rapid test:
  - 93% sens, 98% spec compared to culture
- Awaiting comparison to TMA for TV

New TV research in Adolescents

- Incidence, Natural History, and Response to Treatment of *Trichomonas vaginalis* among Adolescent Women
  - Van der pol, 2005
- Association of sexual behavior and STIs with duration of genital HPV
  - Shew, 2006

Methods - Participants

- Women receiving health care in three primary health clinics
- Ages 14 to 17 years at enrollment
- Not pregnant at the time of enrollment


weekly swabs
weekly swabs
weekly swabs
weekly swabs
weekly swabs
3
6
9
15
18
21
Enroll
12
24
27
Interview
Vaginal/Cervical Specimens

Definitions – *T. vaginalis* Infection

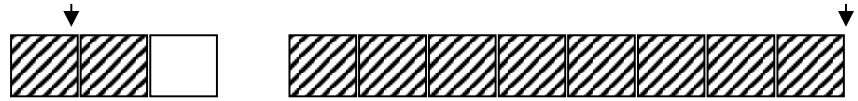
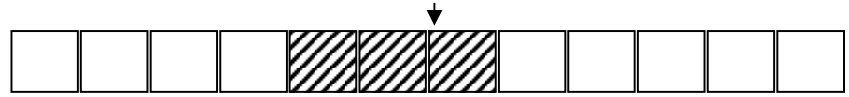
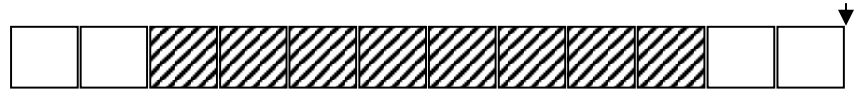
- Tv by PCR- TVK (Amplicor)
- Positive sample obtained during enrollment or quarterly clinic visit
- Two positive weekly samples within a single 12-week period
- Single weekly positive visit with additional corroboration (i.e., positive saline wet mount)

Results

- 268 women enrolled
- 245 women with at least 1 follow-up
- 349 women-years of follow-up

Prevalence & Incidence

- 57/245 (22%) with prevalent/incident infection
- 16/268 (6%) infected at enrollment (prevalent)
- 45/245 (18%) with at least one incident infection
- 18/57 (32%) with multiple infections during follow-up

Pattern	Interpretation
1	 Treated infection
2	 Possible treatment failure
3	 Possible reinfection
4	 Possible intermittent shedding
5	 Incident infection
6	 Treated incident infection
7	 Incident infections with possible resolution
8	 Possible false-positive PCR

Care Seeking Behaviors and Spontaneous Clearance

- 21 incident infections identified by weekly samples (not identified at the next quarterly visit)
- 11/21 sought treatment
- Median time to treatment =2 weeks
- 10/21= spontaneous clearance? Treatment elsewhere?

Response to Treatment

- Treatment documented during 42 weekly collection periods
- 39/42 (93%) negative within two weeks
- Without treatment, longest duration of infection= 12 weeks

Conclusions

- Prolonged duration of untreated infections
- Rapid disappearance of *T. vaginalis* DNA after treatment

Shew: TV and clearance of HPV

- Longitudinal, weekly samples and quarterly clinical visits, STI testing as described
- HPV typing – PCR-(Roche)
  - 27 types
  - 2 weekly swabs pos for same type= infection
- 49 subjects with 241 HPV infections
- 2458 swabs, 2.2 years of follow-up

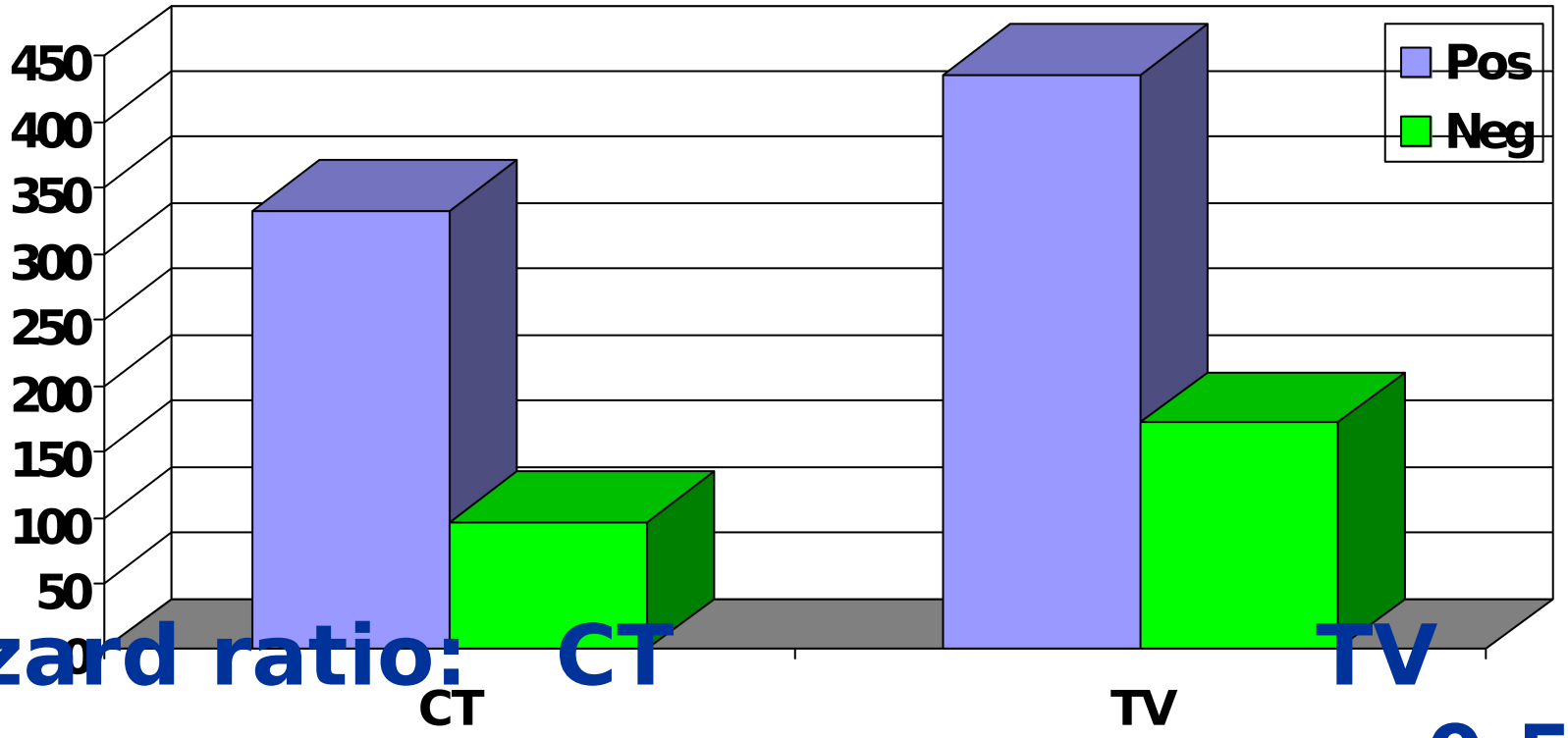
Shew, 2006

TV and clearance of HPV

	Days to clear	Hazard ratio
CT +	CT-	
333	96	0.58 (.31-.89)
TV+	TV-	
436	172	0.32 (.16-.64)

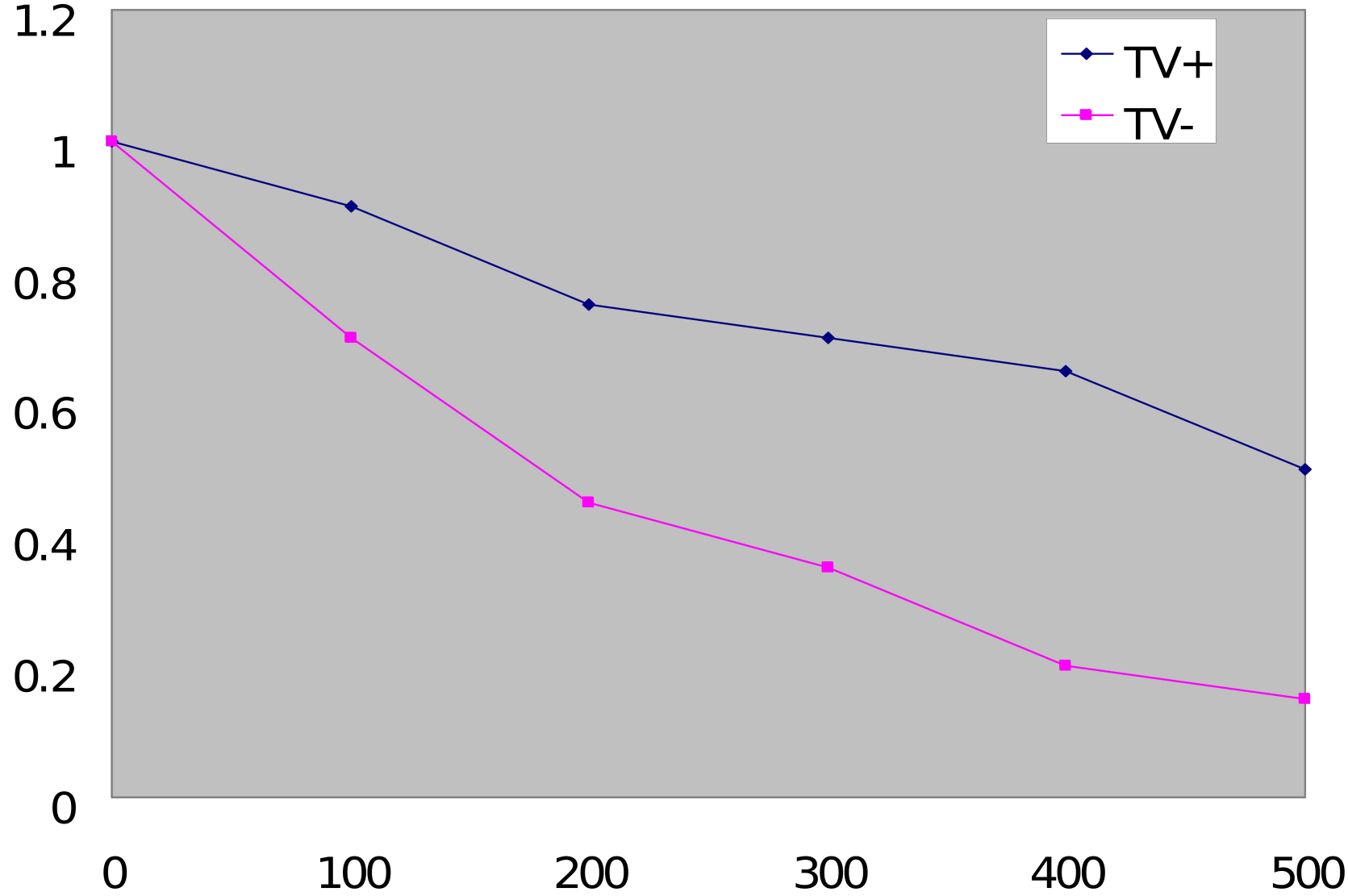
Shew, 2006

Days to clear HPV infection



Hazard ratio: CT . 0.58 (.31-.89) TV 0.32 (.16-.64)

Survival of HPV by TV infection



TV and Cervical Cancer

- Not oncogenic
- Biologic plausibility
  - Alter vaginal ecosystem
  - Chronic inflammation
  - Prolongs HPV (see Shew)
- Host response to chronic inflammation

Implications for Practice

Now what should we do?

Implications for Practice

- Who should be screened?
- Which diagnostic method?
- What will better detection of TV accomplish?

Who should be screened?

- Symptomatic women of any age
  - Vaginal complaints
  - Abnormal appearing discharge
- Asymptomatic women at risk of STDs
  - **Teens**
  - >1 sexual partner
  - Substance abuse
  - Other STIs

What TV test method?

- If wet mounts available and reliable:
  - Wet mount
  - Culture or rapid test for wet mount negative subjects
- If wet mount not available/reliable
  - Culture
  - Rapid test
- If available: PCR/ NAAT

Research directions

- Re-evaluate outcomes using better diagnostic tests
  - PID
  - Obstetric outcomes
  - Cervical neoplasia
  - HIV
  - ?? BV
- Longitudinal studies on effect of TV detection and treatment

Recommended Reading

- Clinical review:

  Soper D. Trichomoniasis: under control or undercontrolled? *Am J Obstet Gynecol.* Jan 2004;190(1):281-290.

- Microbiology

  Petrin D, Delgaty K, Bhatt R, Garber G. Clinical and microbiological aspects of Trichomonas vaginalis. *Clin Microbiol Rev.* 1998;11(2):300-317.

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